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REVIEW

Chemical delivery systems and soft drugs: Retrometabolic approaches of drug design

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Soft drug design;
Angiotensin converting enzyme

Abstract Inclusion of metabolic considerations in the drug design process leads to significant development in the field of chemical drug targeting and the design of safer drugs during past few years which is a part of an approach now designated as Retro metabolic drug design (RMDD). This approach represents systematic methodologies that integrate structure–activity and structure–metabolism relationships and are aimed to design safe, locally active compounds with an improved therapeutic index. It embraces two distinct methods, chemical delivery systems and a soft drug approach. Present review recapitulates an impression of RMDD giving reflections on the chemical delivery system and the soft drug approach and provides a variety of examples to embody its concepts. Successful application of such design principles has already been applied to a number of marketed drugs like esmolol; loteprednol etc., and many other candidates like beta blockers, ACE inhibitors, alkylating agents, antimicrobials etc., are also under investigation.

Contents

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1. Introduction

Chemotherapeutic research started with the identification of lead structures. These lead structures are unique for each target. Lead structures often need to be developed by incorporating desirable safety, efficacy and ADME characteristics required for a "drug". For example- development of cimetidine (drug) and ranitidine (drug) was from brimmed drug candidate and N-α guanyl histamine (drug candidate), that were both developed from histamine (lead) (Ganellin, 1982; Bradshaw, 1993). Thus, we can say that in drug discovery we are concerned to select a suitable drug candidate with promising pharmacological activity for the development process. The main aim of the drug design process is to bring down the toxicity level of a drug candidate with improved activity as well as therapeutic index (Drews, 2000). But unfortunately, as the pharmacological activity of a drug increases, the toxic effects also increase and the therapeutic index remains unchanged. To improve the therapeutic index one has to separate activity and toxicity properties of a drug compound. The toxic or unwanted side effects are produced during the drug design process because new structural moieties are introduced into the drug candidate to enhance its activity and hence, the toxic or unwanted pharmacokinetic properties will further be enhanced during the drug design process. The high activity of a drug candidate is of no use if it has high toxicity as well and the only reason for the low success of a drug design process is the lack of toxicity consideration during such a process. One way to decrease the drug toxicity is to design metabolically stable drugs.

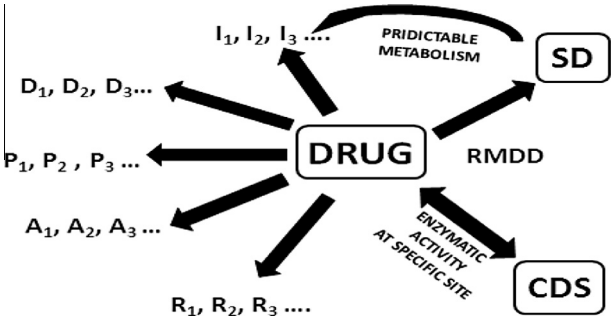

Figure 1 General metabolic pathway of drug and Retrometabolic drug design strategy via soft drug approach and chemical delivery system where D_1, D_2, D_3... are metabolites with similar structure and activity of the parent A1, A_2, A_3... are metabolites with dissimilar structure and activity of the parent compound, P_1, P_2, P_3... are metabolites with different pharmacokinetic profiles, I_1, I_2, I_3... are inactive metabolites and R_1, R_2, R_3... are metabolites which are potentially reactive intermediates.

At one glance, the idea looks very facilitating as one can avoid unwanted toxicity by avoiding the metabolism of the drug and a simpler pharmacokinetic route can be followed by a drug controlled by only renal excretion. These non-metabolic drugs are called as 'hard drugs' (Ariens and Simonis, 1977). But, the idea of designing ideal hard drugs is not achieved till date because living organisms have developed mechanisms to metabolize the endogenous substances as well as for the detoxification (Gillette, 1979; Mannering, 1981). Most metabolic processes aim at the transformation of foreign chemicals into more easily eliminated hydrophobic conjugates (Picot and Macherey, 1996).Thus, it is not enough for a molecule to just have good pharmacodynamic property but pharmacokinetic parameters also play a vital role for a molecule to become a drug because the in vivo administration of a drug becomes a troublesome process as it has to cross a number of biological barriers (Bodor, 1977). The pharmacokinetic factors which affect the in vivo administration of the drug are: absorption, distribution, metabolism and excretion (ADME). Thus, the basis of successful drug discovery is the incorporation of the ADME approach to the process. Out of four pharmacokinetic factors, metabolic studies play an important role in drug discovery because the study of metabolic clearance pathways as the major drug clearance pathway is very important in determining the drugability of the molecule (Bodor, 1984). In early drug discovery processes, the main role of drug metabolism is to provide a basis for choosing the chemical structures and lead compounds with desirable drug metabolism and pharmacokinetic properties but nowadays metabolic studies are mainly

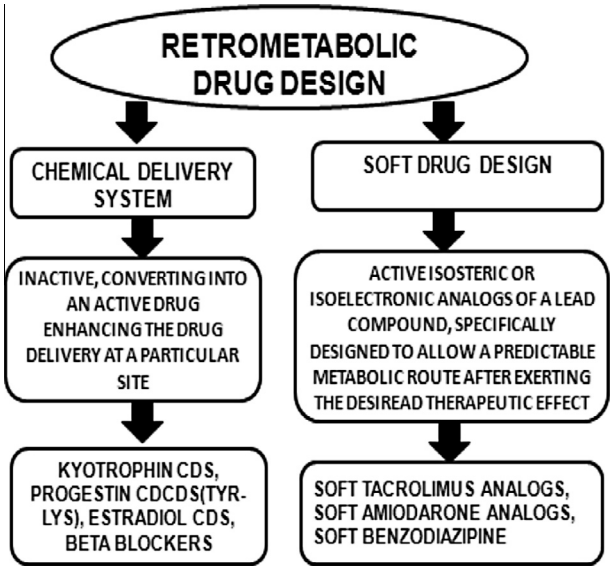

Figure 2 Concept of retrometabolic drug design.

concerned to have a good safety profile of the drug (Bodor and Buchwald, 2000). Thus, it is necessary to take into consideration the metabolic as well as the toxicity profile of a molecule during the drug design process. The metabolism of a foreign compound by a given enzyme in the body can result in the formation of either toxic or non-toxic metabolites. The metabolic conversion of a drug can generate (as shown in Fig. 1):

1. Metabolites with similar structure and activity of the parent drug (D_1, D_2, D_3...).
2. Metabolites with dissimilar structure and activity of the parent compound (A_1, A_2, A_3...)
3. Metabolites with different pharmacokinetic profiles (P_1, P_2, P3...).
4. Inactive metabolites (I_1, I_2, I_3...).
5. Metabolites which are potentially reactive intermediates (R_1, R_2, R_3...).

Therefore, xenobiotics do not always get converted into active or inactive species but also into highly reactive intermediates like epoxides and radicals from non toxic compounds which are responsible for tissue damage. Intrinsic toxicity of a drug candidate which is a combination of biological mechanism based inputs, non-specific chemical based inputs, inputs based on other biological mechanisms like action is mediated by some enzyme system or receptor system (Bodor and Buchwald, 2003).

2. Retrometabolic drug design principle

Inclusion of metabolic considerations in the drug design process leads to significant development in the field of chemical drug targeting and the design of safer drugs during the past few years which is a part of an approach now designated as Retro metabolic drug design (RMDD) (Bodor and Buchwald, 1997). The word 'Retrometabolic' means situated backward or behind in position. These drug design strategies are designated as retrometabolic because in these approaches metabolic pathways are designed going backward as compared to actual metabolic processes. Retrometabolic drug design approach signifies a systematic methodology that combines structure activity and structure metabolism relationships to develop locally active compounds with a safe and enhanced therapeutic index.

Retrometabolic drug design concept involves two approaches so as to improve the therapeutic index of drug candidates, chemical delivery system (CDS) and soft drug (SD) approach as shown in Fig. 2. Chemical delivery system is defined as one in which a biologically inert molecule is converted into an active drug by a number of steps enhancing the drug delivery at a particular organ or site (Bodor and Kaminski, 1987). Soft drugs are the active isosteric or isoelectronic analogs of a lead compound, a structure specifically designed to allow a predictable metabolic route after exerting the desired therapeutic effect (Bodor, 1982). The drug targeting by CDS as well as SD approach requires the enzymatic system but the principles of CDS and SD are altogether different. On one hand, CDS is inactive and requires a number of steps to get converted into the active drug, SDs are active by nature and are deactivated by a predictable and controllable metabolic route via a single detoxification step. For a CDS, the drug is present at the site due to enzymatic reaction and is absent in the rest of the body while in the case of SDs, the drug is present at the site and absent in the other sites of the body because of enzymatic reactions at those sites of the body (Bodor, 1994, 1995).

2.1. Chemical delivery system (CDS)

Chemical delivery system is designed by recognizing specific enzymes exclusively at the site of action. The concept of CDSs has already been applied in a variety of drug targeting strategies, achieving successful delivery to the brain, eye and other organs of the body (Bodor et al., 1981; Bodor, 1985a, 1987, 1990, 1999; Bodor and Brewester, 1991; Bodor and Buchwald, 1998). The drug targeting through the CDS approach includes

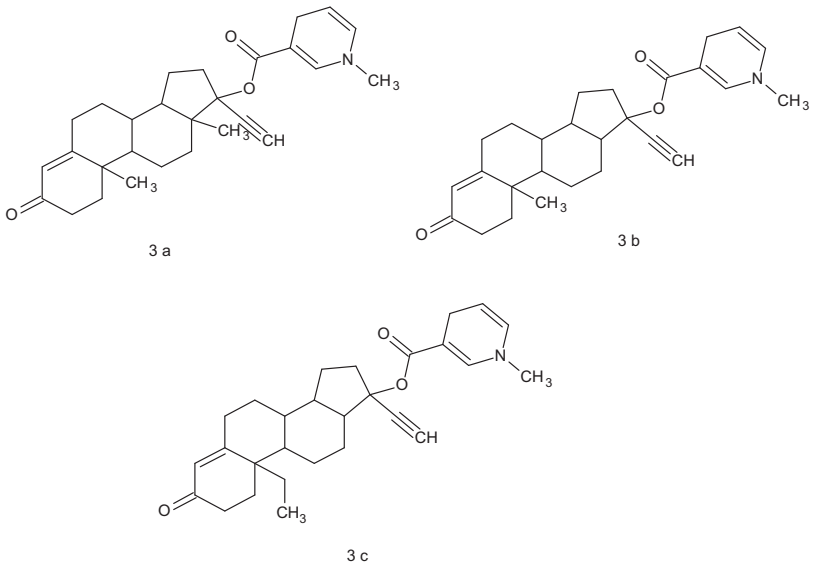

Figure 3 Progestin chemical delivery system.

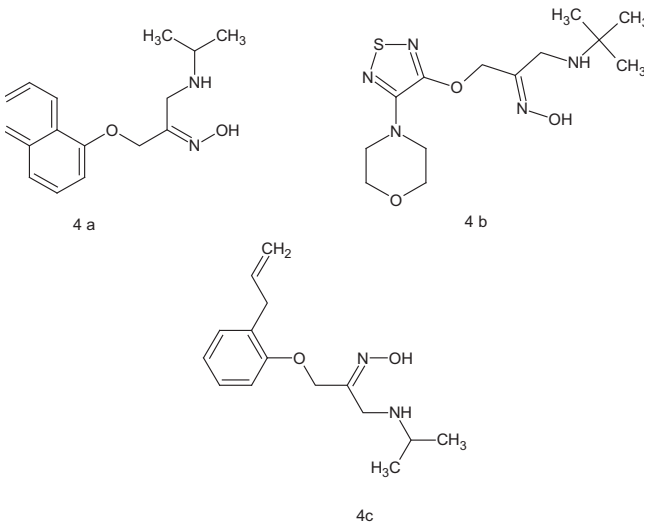

Figure 4 Ketoxime analogs of β-adrenergic blockers.

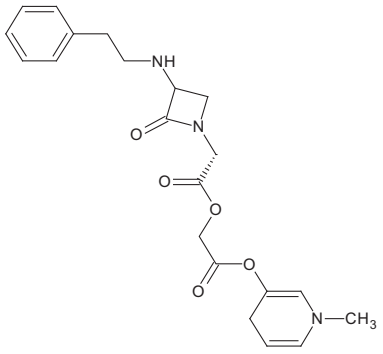

Figure 5 Dihydropyridine-pyridinium salt redox carrier-based chemical delivery system for benzylpenicillins.

a system that requires a step of chemical reactions to yield the active drug. The system should have a covalent link between the drug and carrier and one bond needs to be broken. The CDS concept was evolved from the prodrug concept (Albert, 1958; Stella, 1975) but both the concepts are essentially different. Prodrugs contain one or more moieties which protect or enhance the overall delivery of the drug, but they lack targeting (Balant and Doelker, 1995). In a chemical delivery system, the drug is converted into the inactive form by two moieties, one is a target which is responsible for site specificity and targeting, the other is the modifier function, can be more than one in number, for the protection of certain functional groups and to prevent the drug from unwanted metabolic reactions (Bodor, 1985b).

A number of CDS have been designed to have successful delivery of the medicaments to some organs.

Progestin chemical delivery system, **3a**–**c** was developed to transport gonadal steroids like estradiol and testosterone to the CNS to avoid its peripheral untoward actions like hypertension and weight gain (Fig. 3) (Brewester et al., 1986).

Due to poor ocular bioavailability of the drug following systemic administration, the preferred route to treat most of the ocular problems is the topical administration of the drug attributed to hindrance by Blood retinal barrier (BRB), which is as effective as the Blood brain barrier (BBB). The local administration of drug to the eye too suffers with the problem of bioavailability owing to some precorneal factors like tear turnover, physicochemical mismatch with cornea and drainage of the drug from the eye. So, in an effort to enhance the bioavailability of the drug to the eye through systemic circulation, ketoxime analogs of β-adrenergic blockers, **4a** & **b** were developed as antiglaucoma agents with high lipid solubility and reduced systemic toxicity than the oxime analogs (Bodor et al., 1988a). A new site specific chemical delivery system **4c** for alprenolol was also designed (Fig. 4) (Bodor and Elkouss 1991).

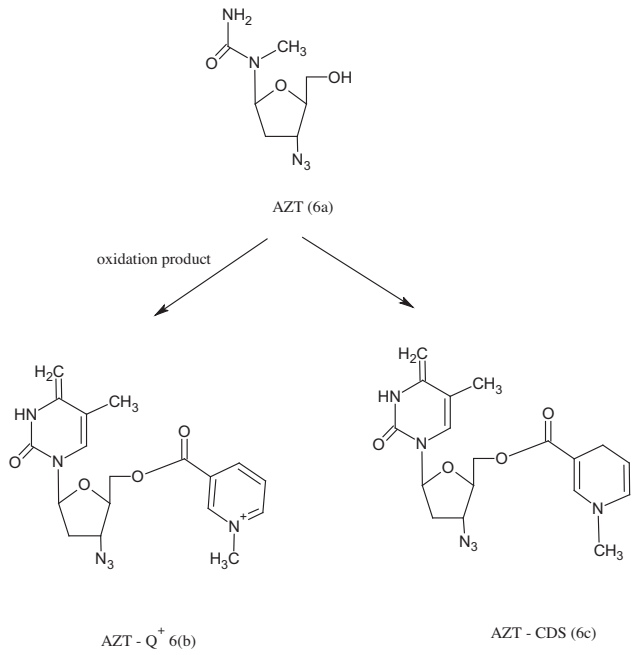

Figure 6 AZT-CDS.

Penicillins and cephalosporins are used widely to treat many bacterial infections because of low toxicity and low minimum inhibitory concentration over other β-lactam antibiotics but all have a problem related to their transportation across BBB as well as showing a rapid elimination rate through body. But benzylpenicillins are still the drug of choice not only to treat bacterial meningitis but also other infections of the brain, such as AIDS-related brain syphilis, brain abscesses, Lyme's disease etc. because of remarkable BBB penetration. A dihydropyridine-pyridinium salt redox carrier-based chemical delivery system for benzylpenicillins was developed (Fig. 5) (Pop et al., 1991).

Zidovudin (AZT), **6a** exerts significant activity against HIV. But, the restricted transport of this drug through BBB results in low drug concentration in the CNS and only marginal retroviral activity of zidovudin is detected. The CDS, **6c** of zidovudin has been developed with improved CNS uptake of the drug. The AZT-CDS was found to be three to ten times active than AZT in the brain. Owing to this target based approach, AZT-CDS was not only more effective in inhibiting the HIV replication but it was also less toxic to the host lymphocytes than AZT (Fig. 6) (Brewester et al., 1995).

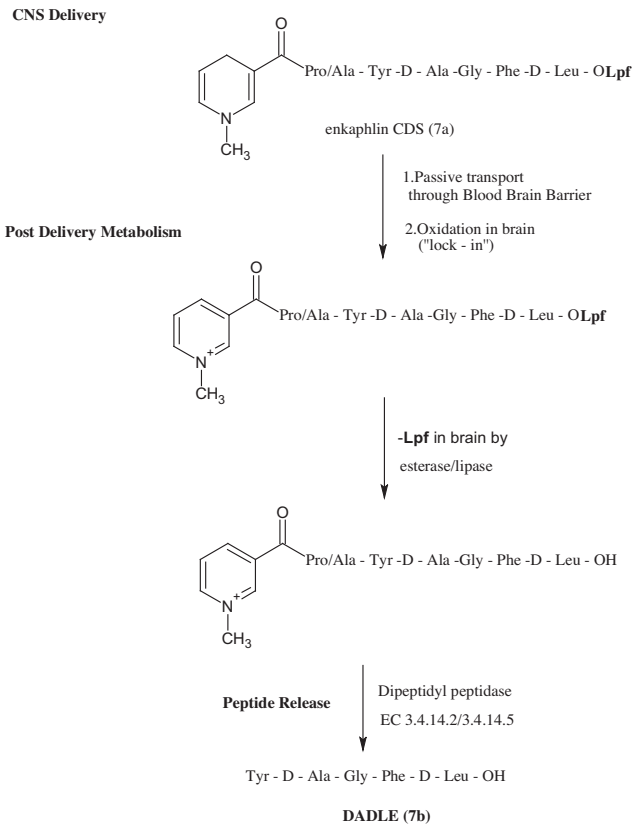

Figure 7 Enkaphlin analog CDS.

A CDS has been developed for the targeted delivery of enkaphlin analog, **7a** to the brain. In this design, a synthetic leucine-enkaphlin analog, DADLE, **7b** a well known opioid agonist, is surrounded by functional groups that protect the peptide from the action of peptide degrading enzymes and provide sufficient lipophilicity for penetration through BBB (Fig. 7) (Prokai et al., 1996).

The design, synthesis and pharmacological assessment of the brain targeted chemical delivery system, **8a** for a kyotrophin analog (Tyr-Lys) has also been developed. The spacer used in this design can be proline, **8b**, proline- proline, **8c** or proline- alanine, **8d** (Fig. 8) (Chen et al., 1998).

Oxime, **9a** or methoxime, **9b** analogs have been designed as potential antiglaucoma agents of known β-adrenergic blockers (Fig. 9) (Bodor and Buchwald, 2005).

A novel carrier system for the sustained drug delivery to the brain, **10a** & **b** was synthesized as a group of 1-malonyl-1,4-dihydropyridine derivatives. This CDS ensures a definite shelf life, a good rate of oxidation, non-neurotoxic and easy excretion from the brain (Fig. 10) (Hassan et al., 2009).

A new CDS of BZD was designed as the GABA agonist with improved aqueous solubility. These analogs preserve the potency as well as the agonist profile (Fig. 11) (Jeffrey et al., 2002).

Centrally acting TRH analogs are synthesized by solid phase Zincke Reaction. The prodrugs of these analogs were obtained by a reduction mechanism and after enzymatic oxidation and sustained release, degradation resistant analogs were found with enhanced bioavailability in the brain (Fig. 12) (Katalin et al., 2002).

A most recent CDS **13a**–**c** was designed to increase the stability of 1,2-dihydropyridine derivatives toward oxidation and hydration reactions (Fig. 13) (Ĺenäıg et al., 2009).

2.2. Soft drug design

Soft drugs are the isosteric or isoelectronic analogs of a lead compound that have a predictable and controllable metabolic route so that the toxic effects of the drug could be overcome with an improvement in the therapeutic index of the drug. The desired activity of the soft drugs is generally local and they are applied on or near the site of action. Thus, the soft drugs produce their pharmacological effect locally, but their distribution away from the site of action results in metabolic deactivation, which avoids undesirable activity and toxicity. *Bodor* and *Kamenski* first introduced the Soft Drug concept in 1980 and since then five major strategies of soft drug design have been identified which are as follows-

1. Soft analogs
2. Soft drugs based on the inactive metabolite approach
3. Controlled release endogenous agents
4. Activated soft compounds
5. Active metabolite base soft drugs

3. Key strategies for soft drug design

3.1. Soft analogs

These classes of compounds are the structural analogs of the known active drugs which have an in-built metabolically sensitive moiety which is responsible for their one step controllable detoxification. The sensitive moiety is so designed that the detoxification is achieved soon after the drug has shown its desired pharmacological activity, not allowing any other route of metabolism to take place.

The soft analog design strategy involves some basic principles as listed below:-

1. New soft analogs are isosteric/isoelectronic with the lead compound.
2. The inbuilt metabolically sensitive moiety is such that it should not hinder the pharmacological activity of the drug.
3. The metabolically sensitive moiety is located within the molecule in such a manner that the overall physical, physiochemical, steric and complementary properties of the soft analog are very close to the lead compound.
4. The inbuilt metabolically sensitive moiety is preferably the only route of metabolism.
5. There is predictable metabolism that can be controlled by structural modifications.
6. The resulting metabolic products are non toxic or with low toxicity
7. There is no need of any enzymatic process leading to highly active intermediates, the oxidative metabolism must be replaced by the hydrolytic process.

The designed route of metabolism should produce structural change in the molecule, which is responsible for its complete deactivation. Simple conjugation or simple one function

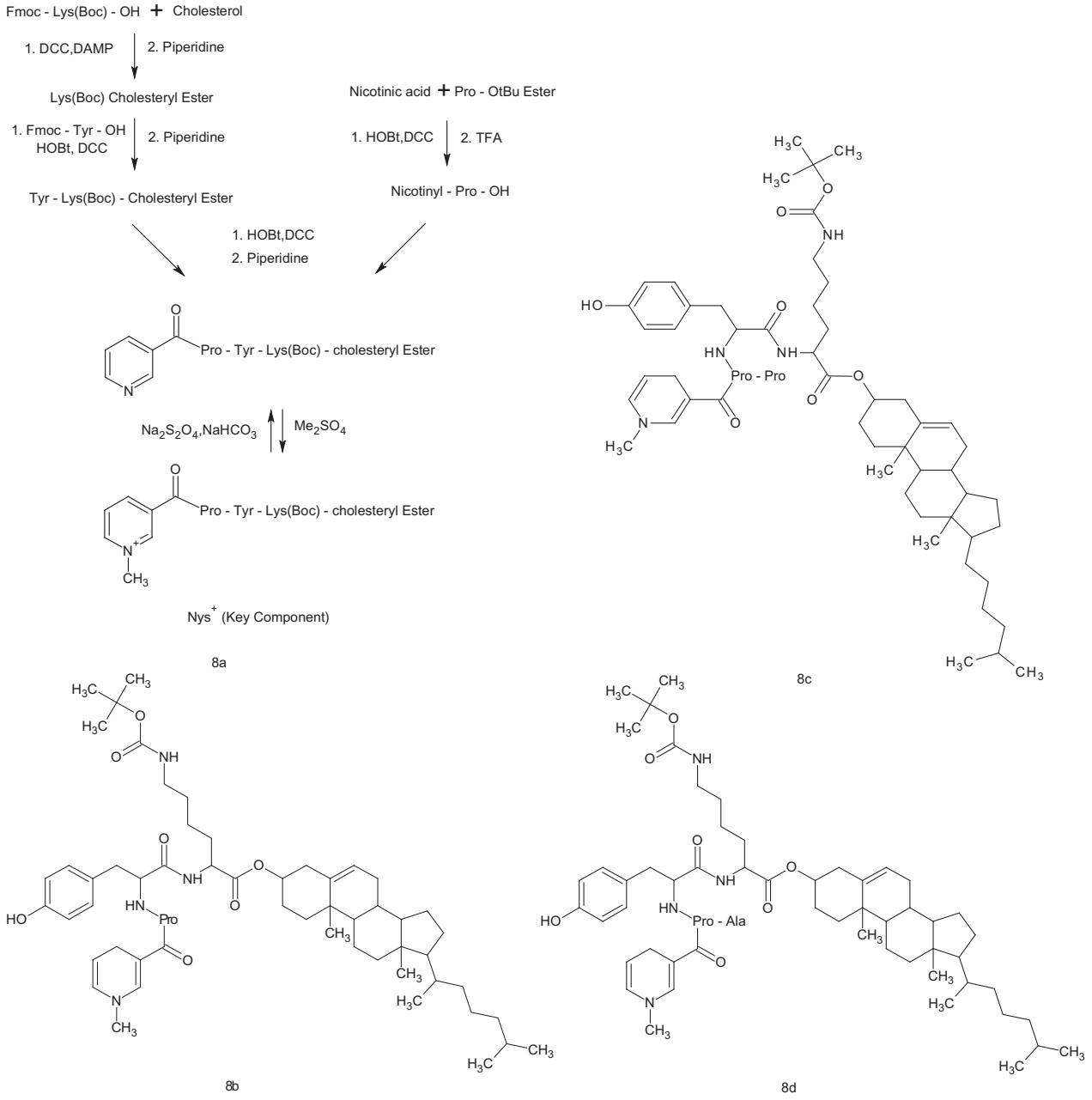

Figure 8 Brain targeted chemical delivery system.

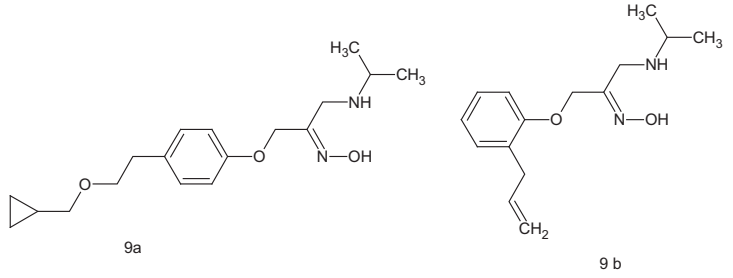

Figure 9 Oxime and methoxime analogs potential antiglaucoma agents of known β-adrenergic blockers.

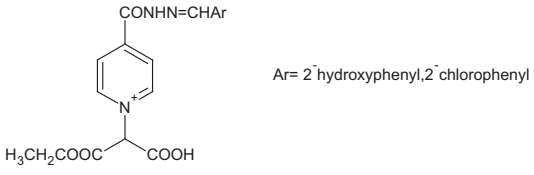

Figure 10 A novel 1-malonyl-1, 4-dihydropyridine carrier system for the sustained drug delivery to the brain.

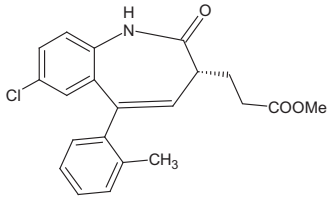

Figure 11 CDS of BZD as GABA agonist.

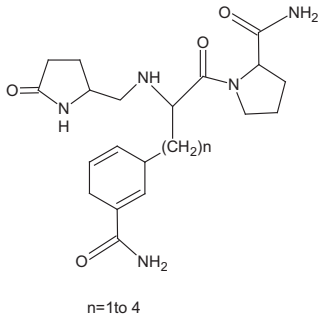

Figure 12 Centrally acting TRH analogs.

introduction into the molecule leads to complete deactivation of the molecular structure.

The design of labile quaternary ammonium salts, **14a**–**c** as soft antimicrobials with improved pharmacokinetic properties and less toxic effects was reported (Fig. 14) (Bodor et al., 1980a).

Some soft quaternary ammonium L-carnitine esters, **15a** & **b** with broad spectrum antimicrobial activity were reported (Fig. 15) (Calvani et al., 1998).

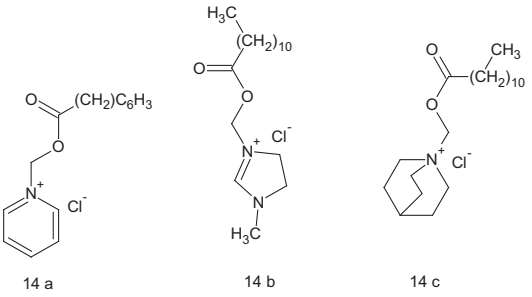

Figure 14 Labile quaternary ammonium salts as soft antimicrobials.

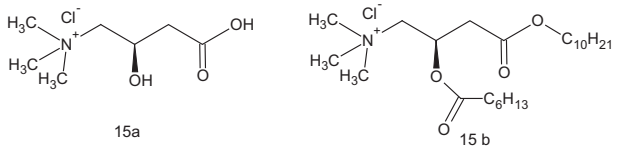

Figure 15 Soft quaternary ammonium L-carnitine esters.

Soft analog approach was used in order to synthesize the soft analog of propantheline against indomethacin-induced gastric ulceration and in inducing mydriasis. The increased metabolic lability with equipotency of these soft analogs is an advantage over the propantheline which had many side effects like eczema, erythrema etc. (Fig. 16) (Brouillette et al., 1996).

Some short acting antiarrhythmic agents, **17a**–**e** were synthesized as a replacement of the antiarrythmic drug lidocain which had a problem of reduced systemic and central nervous effects (Fig. 17) (Stout et al., 1989).

Some muscranic receptor antagonists, **18a** & **b** were reported as a class of anticholinergic agents which are soft analogs of some known anticholinergics with local but practically no systemic activity to show antispasmodic, antisecretary and mydriatic effects. These compounds particularly act as inhibitors of eccrine sweating (Fig. 18) (Bodor et al., 1980b).

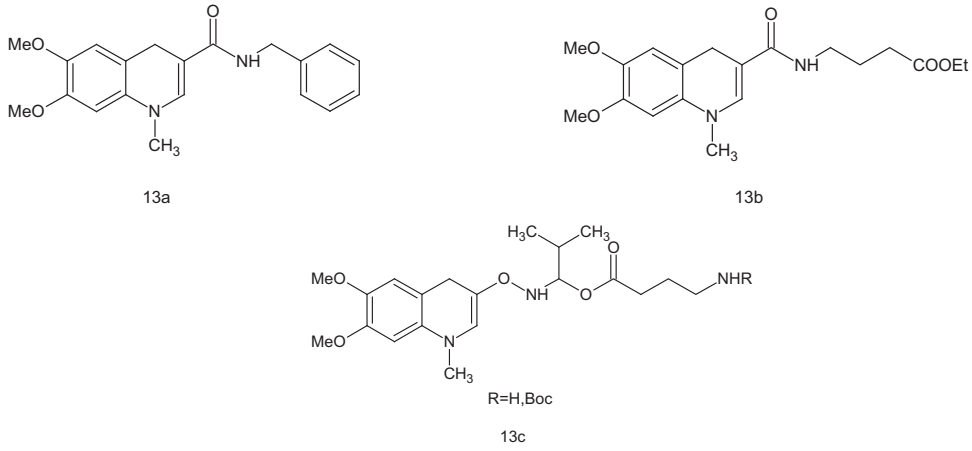

Figure 13 Design of the redox CDS.

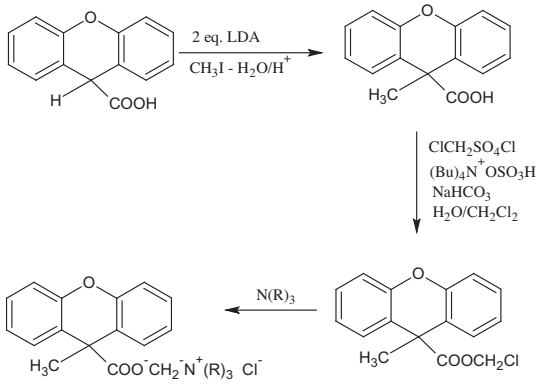

Figure 16 Soft analog of propantheline.

3.2. Inactive metabolite approach

This is one of the most useful and successful strategies for designing safe and selective soft analogs. It also involves the metabolism of active species. This approach deals with the structural modifications in the inactive, excreted metabolite of an active drug in order to allow the metabolic reconversions to occur in a facile, one step and controllable manner, with a return to the very inactive metabolite from which the design began.

The strategies to be applied for inactive metabolite based soft drug approach are:-

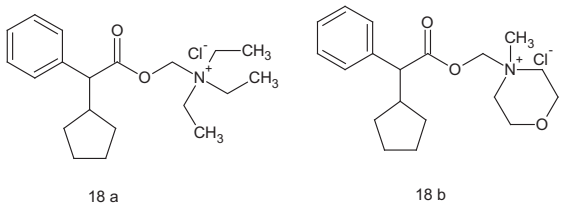

Figure 18 Soft analogs of some known anticholinergics.

1. The design starts with the inactive, excreted metabolite of the active drug.
2. The specific chemical modifications of the inactive metabolite which makes its structure isosteric or isoelectronic to the active metabolite of the drug or the active drug itself.
3. New structure is such that there is a one step conversion into the inactive metabolite without any metabolic conversions.
4. By structural modifications we can control the metabolic routes as well as specific binding and transport properties of the new soft compounds.

Anticholinergics are the muscranic receptor antagonists which inhibit the effects of acetylcholine by blocking its binding to the muscranic receptors present at neuroeffector sites on smooth muscles, cardiac muscles and gland cells in peripheral ganglia and in CNS. These anticholinergics are used in the treatment of asthma, prevention of motion sickness, mydriasis, Alzheimer's disease, Parkinson's disease and disorders of

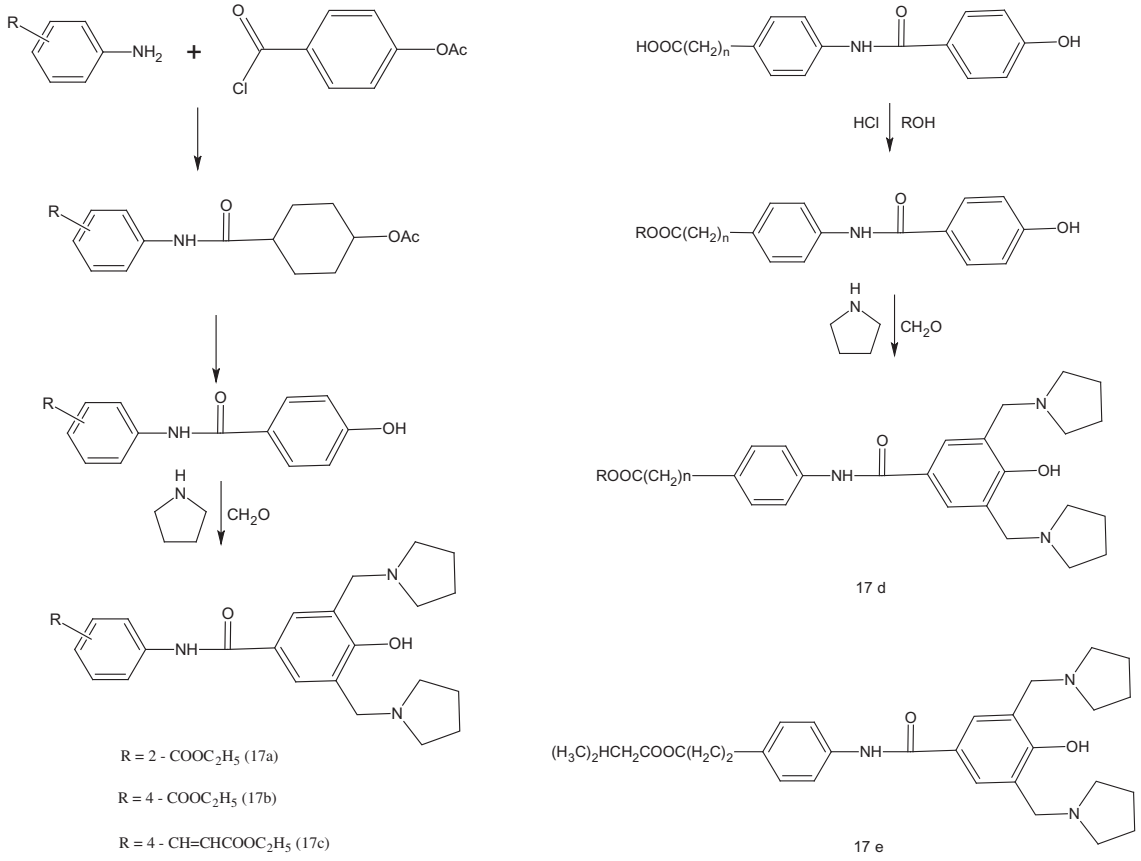

Figure 17 Short acting antiarrythmic agents.

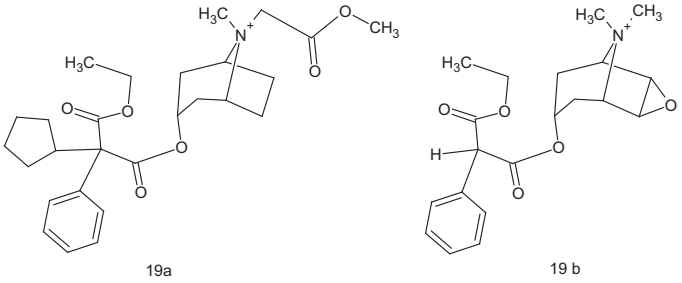

Figure 19 Soft anticholinergics.

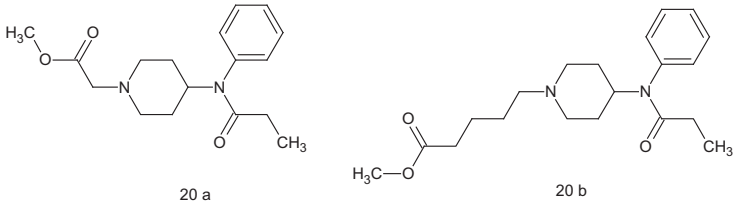

Figure 20 Highly potent synthetic steroids.

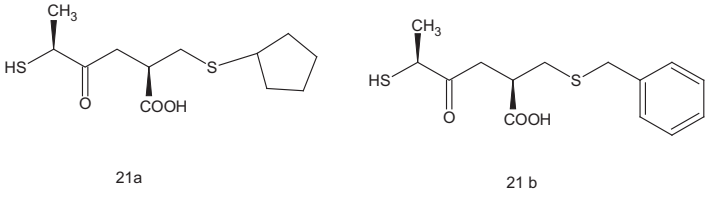

Figure 21 Opioid analgesics.

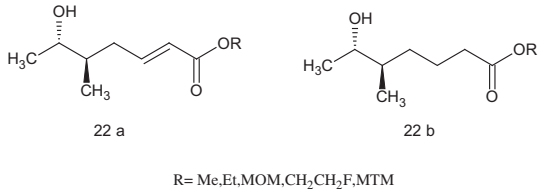

Figure 22 Ultra short acting antiarrythmics.

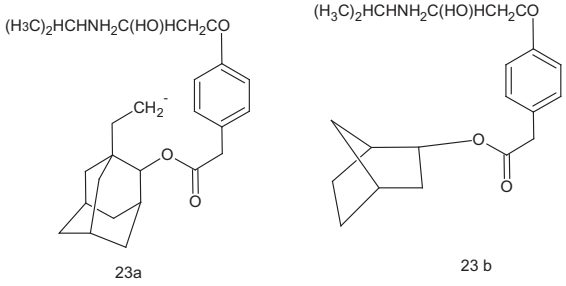

Figure 23 β-Adrenoreceptor antagonists.

intestinal motility, cardiac function and urinary bladder functioning. Soft anticholinergics, **19a** & **b** were designed using an inactive metabolite based soft drug approach (Fig. 19) (Buchwald and Bodor, 2006).

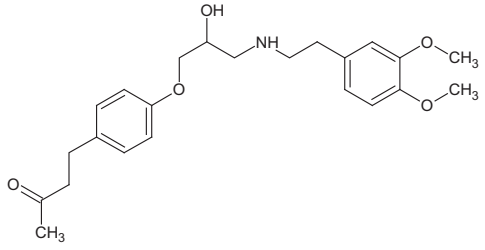

Figure 24 Cardio selective series of ultra short acting β-blockers.

The design of analogs of highly potent synthetic steroids, **20a** & **b** with expected hydrolytic stability has been reported to ensure the topical administration of these compounds (Fig. 20) (Little et al., 1999).

Focusing on shorter outpatient surgical procedures inactive metabolite based approach was used to design opioid analgesics, **21a** & **b** with prolongation of pharmacological effects upon infusion (Fig. 21) (Feldman et al., 1991).

A number of ultra short acting antiarrhythmics has been designed, **22a** & **b**. Their advantage over long acting agents is that they rapidly achieve the steady state plasma concentration and therapeutic effects because of short biological half life (Fig. 22) (Baxter et al., 1992).

The design of β-adrenoreceptor antagonists, **23a** & **b** derived from metoprolol has been reported. This includes

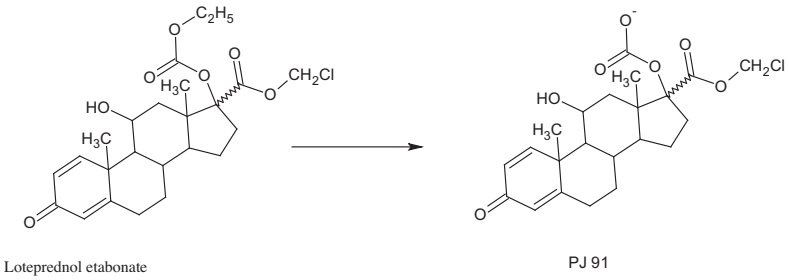

Figure 25 PJ 91.

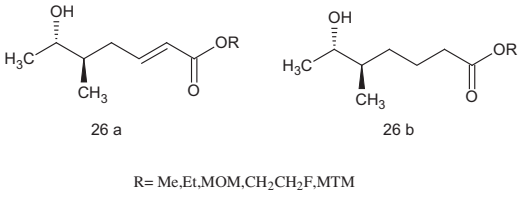

Figure 26 Cyclosporin A analogs.

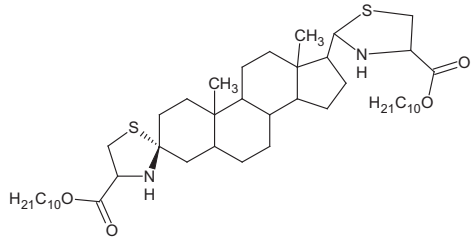

Figure 27 Thiazolidine type derivatives of progesterone.

controllable and one-step conversion to the active metabolite with effective antiglaucomal activity (Fig. 23) (Erhardt et al., 1982).

Another cardioselective series of ultra short acting β-blockers were previously reported with long duration of action by using inactive metabolite based soft drug approach (Fig. 24) (Bodor et al., 1988b).

The synthesis of loteprednol etabonate was described which gets converted into PJ 91. The drug is locally acting and with no systemic side effects. This drug was developed specially for topical use but because of low oral availability, this drug can also be used for pulmonary and ocular delivery (Fig. 25) (Hochhaus et al., 1992).

A rapid and efficient semi synthetic route to a family of Cyclosporin A analogs, **26a** & **b** were investigated exploiting the olefin metatheses reaction (Fig. 26) (Lazarova et al., 2003).

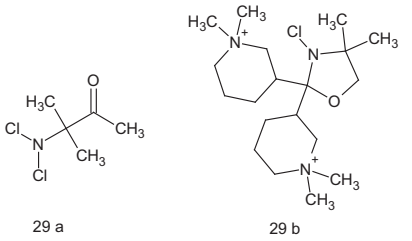

Figure 29 Soft N-Chloramines.

3.3. Controlled released endogenous agents or natural soft drugs

Natural hormones and other biologically active agents such as neurotransmitters can be considered as natural soft drugs since our body has fast and efficient routes of their metabolism and their metabolism does not result in the production of toxic metabolites, particularly if they are not present in concentrations above the normal level. Thus, the design of soft drugs from these endogenous agents can be done by adopting the prodrug-soft drug combination also called as the pro-soft drug approach. This will provide a sequence of-Inactive delivery-protective form-active soft drug-inactive metabolites via non toxic intermediates.

Progesterone and testosterone are natural soft drugs but they have a problem related to their metabolism. They metabolize very quickly. This problem can be overcome by developing a delivery system for these drugs by the design of thiazolidine type derivatives of progesterone and testosterone (Fig. 27) (Bodor and Sloan, 1982).

3.4. Activated soft compounds

These compounds do not include the analogs of known drugs. The process involves starting with a known non toxic compound in which the pharmacologically active moiety is introduced which is responsible for its pharmacological activity.

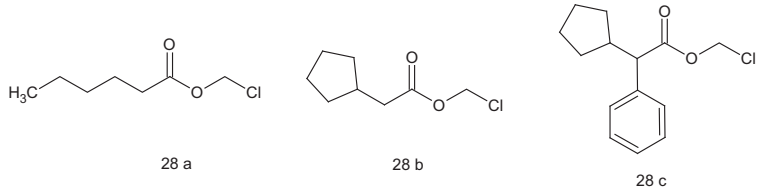

Figure 28 Soft alkylating compounds.

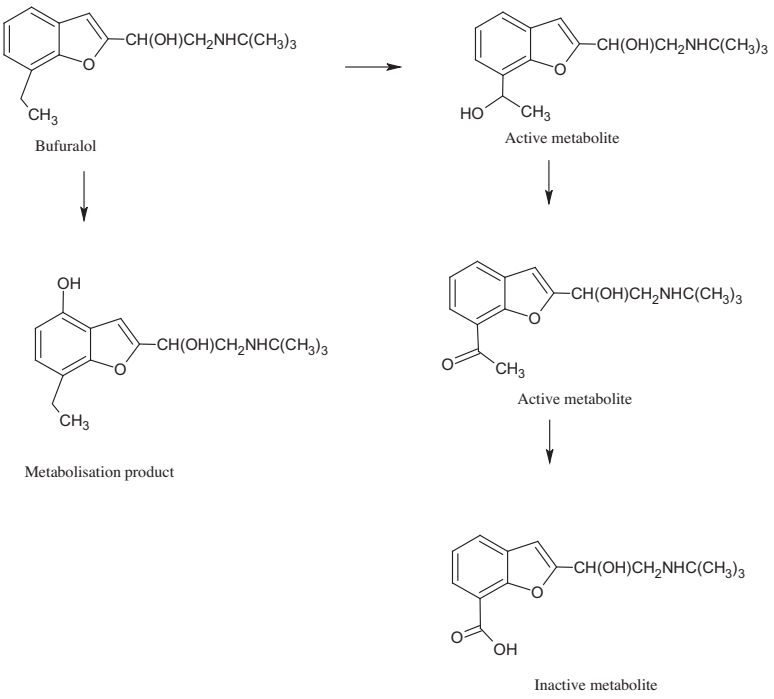

Figure 30 Active metabolite based soft drugs.

The activated form is then changed to the non active, non toxic starting molecule after performing its therapeutic role by a one step detoxification reaction

Some soft alkylating compounds, **28a–c** as active, site specific/site selective potential antitumor agents were reported. These agents are characterized by a predictive in vivo metabolic destruction to non-toxic metabolites after the achievement of the therapeutic role (Fig. 28) (Bodor and Kaminski, 1980).

A number of soft N-chloramines, **29a** & **b** containing nitrogen-chlorine bonds of different polarity have also been synthesized (Fig. 29) (Kaminski et al., 1976).

3.5. Active metabolite based soft drugs

It is well known that most drugs undergo stepwise metabolic degradation via oxidative metabolic routes to yield structural analogs having similar activity like that of the parent drug. These metabolic routes not only put a burden on the body's oxidative enzyme system but also produce a number of therapeutically active compounds with different selectivity, binding, distribution and elimination properties. But the development of safe and active general dosing of these compounds is practically impossible because of a variety of combinations of active species in different individuals depending upon their enzyme system as well as the presence of other compounds requiring same enzymes.

As this class refers to the metabolic products of a drug that retains significant activity as that of the parent drug, the judicious selection of an active metabolite can yield a potent drug that will undergo one step deactivation and thus detoxification. The one step deactivation is because the active metabolite is already in highest oxidation state. In other words we can say, the drug of choice should be the active metabolite which is in the highest oxidation state (Fig. 30) (Hwang et al., 2000).

4. Conclusion

For a drug design process it is not only important to increase the activity but also to reduce the side effects. Retrometabolic drug design principle aims to design new, safe drugs with an improved therapeutic index and lesser side effects by integrating structure activity and structure metabolic relationships. Soft drug design and Chemical delivery system are the two approaches of retrometabolic drug design. Both approaches rely on a known active lead and they both can result in an approvable drug product than other strategies of drug design.

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